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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/805,240	03/14/2001	Hideki Kambara	HIRA.0011	1304

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EXAMINER	
LEWIS, PATRICK T	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 06/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/805,240	KAMBARA ET AL.	
	Examiner	Art Unit	
	Patrick T. Lewis	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18,20,21 and 24-26* is/are pending in the application.

4a) Of the above claim(s) *1,2,11-14 and 24-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-10,15-18,20 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Invention II (claims 3-10 and 15-23) in Paper No. 4 dated October 9, 2002 is acknowledged.

2. Claims 1-2, 11-14, and 24-26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 4.

Objections/Rejections Set For the in Office Action dated January 14, 2003

3. Claims 3-10 and 15-23 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 3, 17-18, and subsequent dependent claims, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Regarding claims 5, 9, and 19, the phrase "can be" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Regarding claim claims 15-21, said claims depend from claim 11. Claim 11 incorporates the phrase "or the like" which renders the claim(s) indefinite because the claim(s) include(s) elements not actually disclosed (those encompassed by "or the

like"), thereby rendering the scope of the claim(s) unascertainable. See MPEP § 2173.05(d).

Regarding claim 22 and subsequent depending claims, the phrase "or the like" renders the claim(s) indefinite because the claim(s) include(s) elements not actually disclosed (those encompassed by "or the like"), thereby rendering the scope of the claim(s) unascertainable. See MPEP § 2173.05(d).

In claim 23, the parenthetical phrase "(DNA samples)" renders the claim indefinite because it is unclear whether the limitation(s) enclosed in parentheses are part of the claimed invention. See MPEP § 2173.05(d).

The terms "dNTP", "ddNTPs", and "CCD" have not been, in the absence of a clear, precise definition; claims incorporating either or both terms are rendered indefinite in all occurrences.

4. Claims 3-10 and 15-23 were rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Ronaghi et al. *Science*, (**1998**), vol. 281, pages 363-365 (Ronaghi) and Laugharn, Jr. et al. U.S. Patent 6,245,506 B1 (Laugharn).

Claims 3-10 and 15-21 are drawn to a system to obtain DNA sequence information in which pyrophosphate produced upon synthesizing a strand complementary to a template DNA is converted into ATP which is reacted with luciferine in the presence of an enzyme and the complementary strand synthesis is monitored by detecting the resulting chemiluminescence, said system being characterized by comprising a means for supplying four kinds of dNTP into a reaction vessel via independent capillaries or narrow grooves which can be in contact with a reaction

solution, by pressurizing or by a liquid transfer system. Claims 22-23 are drawn to a system characterized in that a DNA to be used as a template for complementary strand synthesis is immobilized onto a solid surface, pyrophosphate produced upon synthesizing complementary strand which is hybridized with the DNA is converted into ATP which is reacted with luciferine by luciferase, and he DNA base sequence is monitored by detecting the resulting chemiluminescence, said system being characterized by comprising a means to remove primers and complementary strand synthesis products or to stop the extension reaction by adding ddNTPs after the first sequencing process using the primers, to freshly inject primers and enzymes , and to subsequently carry out the second DNA sequencing process, and providing a means to carry out this process repeatedly, if necessary.

Ronaghi teaches that natural nucleotides can be used to obtain efficient incorporation during a sequencing-by-synthesis protocol. The detection was based on the pyrophosphate (PPi) released during the DNA polymerase reaction, the quantitative conversion of PPi to ATP by sulfurylase, and the subsequent production of visible light by firefly luciferase. In the DNA sequencing method, four nucleotides are added stepwise to the template hybridized to a primer. The PPi released in the DNA polymerase-catalyzed reaction is detected by the ATP sulfurylase and luciferase in a coupled reaction. The added nucleotides are continuously degraded by a nucleotide-degrading enzyme. After the first nucleotide has been degraded, the next nucleotide can be added. Repeated cycles of deoxynucleotide addition are performed. The amount of light produced in the luciferase-catalyzed reaction can readily be estimated

by a suitable light-sensitive device such as a luminometer or a CCD (charge-coupled device) camera. With this method, parallel processing of large numbers of samples can easily be envision with the use of high-density microtiter plates and microinjector technology. An automated instrument has recently been developed based on the precise delivery of submicroliter volumes of the four nucleotides by "ink-jet" technology into a microtiter plate coupled with simultaneous detection of all samples by a single CCD unit.

Ronaghi differs from the instantly claimed invention in that: 1) Ronaghi does not teach how the dNTP is supplied and 2) Ronaghi does not teach the dimensions of the caplillaries. However, these deficiencies would have been obvious to one of ordinary skill in the art when Ronaghi is combined with Laugharn.

Laugharn teaches an integrated sequencing device (column 2, lines 11-25). The invention features an integrated device for sequencing a polymeric biomolecule, including: a reaction vessel that includes a reaction zone and a detection zone; a solid support in the reaction zone for chemical attachment of the polymeric biomolecule; an enzyme that catalyzes the removal of one monomer unit at a time from one end of the polymeric biomolecule; a probe for sensing a characteristic (e.g., fluorescence, mass, impedance, optical, voltammetric or amperometric properties, etc.) of the released monomers positioned within the detection zone of the reaction vessel; and a pressure control device (e.g., piezoelectric crystal-driven pressure modulation, thin-film-driven pressure modulation, electronic, pneumatic, hydraulic, magnetostrictive, etc.) that controls the pressure at least in the reaction zone of the reaction vessel. The device

can include multiple probes within its detection zone, allowing it to sense a characteristic of a multiplicity of monomers (e.g., for parallel analysis of multiple single molecule sequencing reactions) (column 2, lines 47-62). The probe can be, for example, an optical fiber for fluorescence detection, a fluorescence microscope (e.g., CCD-based or confocal), an infrared or Raman spectrometer, a fluorescence polarimeter, an enzymatic biosensor, or a mass spectrometer. The polymeric biomolecule can be a nucleic acid or polypeptide. At least some of the monomers of the polymeric biomolecule can be labeled with fluorescent tags. Laugharn teaches the diameter of the capillaries as being 0.5 mm (column 10, lines 62-66).

It would have been obvious to one of ordinary skill in the art at the time of the invention to supply the dNTP via capillaries using a pressure control device since Laugharn teaches such. The choice of using capillaries 0.2 mm in diameter is well within the purview of the skilled artisan and is seen as a choice of experimental design. The capillary diameter is not a result-effective variable. In the absence of evidence to the contrary, the skilled artisan would have a reasonable expectation of success in obtaining a DNA sequence utilizing capillaries of 0.5 or 0.2 mm. Thus, the instantly claimed system is prima facie obvious.

Applicant's Response dated March 31, 2003

5. In the Response filed March, 2003, the specification was amended; claims 3-10, 15-18, and 20-21 was amended; and claims 19 and 22-23 were canceled and claims. Applicant presented arguments directed to the rejection of claims 3-10 and 15-23 under

35 U.S.C. 103(a). Claims 1-18, 20-21, and 24-26 are pending. Claims 1-2, 11-14, and 24-26 are drawn to a nonelected invention. An action on the merits of claims 3-10, 15-18, and 20-21 is contained herein below.

6. Applicant's amendments filed March 31, 2003 have been fully considered and have overcome the rejection of claims 3-10 and 15-23 under 35 U.S.C. 112, second paragraph, as set forth in the Office Action dated December 31, 2002.

7. Applicant's arguments, see pages 4-7, filed March 31, 2003, with respect to the rejection(s)of claim(s) 3-10, 15-18, and 20-21 under 35 U.S.C. 103(a) have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of newly found prior art (Yeung et al. U.S. Patent 6,387,234).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. Claims 3-10, 15-18, and 20-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Ronaghi et al. *Science*, (**1998**), vol. 281, pages 363-365 (Ronaghi) and Yeung et al. U.S. Patent 6,387,234 (Yeung).

Claims 3-10, 15-18, and 20-21 are drawn to a system to obtain DNA sequence information in which pyrophosphate produced upon synthesizing a strand complementary to a template DNA is converted into ATP which is reacted with luciferine in the presence of an enzyme and the complementary strand synthesis is monitored by detecting the resulting chemiluminescence, said system being characterized by comprising a means for supplying four kinds of dNTP into a reaction vessel via independent capillaries or narrow grooves which can be in contact with a reaction solution, by pressurizing or by a liquid transfer system.

Ronaghi teaches that natural nucleotides can be used to obtain efficient incorporation during a sequencing-by-synthesis protocol. The detection was based on

the pyrophosphate (PPi) released during the DNA polymerase reaction, the quantitative conversion of PPi to ATP by sulfurylase, and the subsequent production of visible light by firefly luciferase. In the DNA sequencing method, four nucleotides are added stepwise to the template hybridized to a primer. The PPi released in the DNA polymerase-catalyzed reaction is detected by the ATP sulfurylase and luciferase in a coupled reaction. The added nucleotides are continuously degraded by a nucleotide-degrading enzyme. After the first nucleotide has been degraded, the next nucleotide can be added. Repeated cycles of deoxynucleotide addition are performed. The amount of light produced in the luciferase-catalyzed reaction can readily be estimated by a suitable light-sensitive device such as a luminometer or a CCD (charge-coupled device) camera. With this method, parallel processing of large numbers of samples can easily be envision with the use of high-density microtiter plates and microinjector technology. An automated instrument has recently been developed based on the precise delivery of submicroliter volumes of the four nucleotides by "ink-jet" technology into a microtiter plate coupled with simultaneous detection of all samples by a single CCD unit.

Ronaghi differs from the instantly claimed invention in that: 1) Ronaghi does not teach how the dNTP is supplied and 2) Ronaghi does not teach the dimensions of the caplillaries. However, these deficiencies would have been obvious to one of ordinary skill in the art when Ronaghi is combined with Yeung.

Yeung teaches an integrated multiplexed capillary electrophoresis system for the analysis of sample analytes. The system integrates and automates multiple

components, such as chromatographic columns and separation capillaries, and further provides a detector for the detection of analytes eluting from the separation capillaries (Abstract). The system employs multiplexed freeze/thaw valves to manage fluid flow and sample movement. The system contains a plurality of intake capillaries, each intake capillary in fluid communication with one of a plurality of first junctions (column 2, lines 61-67). The detector comprises a charge-coupled device (CCD) or a charge-injection device (CID) (column 6, lines 60-62). Yeung further teaches the use of said system for sequencing nucleic acids.

It would have been obvious to one of ordinary skill in the art at the time of the invention to supply the dNTP via capillaries using a liquid transfer system since Yeung teaches such. The choice of using capillaries 0.2 mm in diameter is well within the purview of the skilled artisan and is seen as a choice of experimental design. The capillary diameter is not a result-effective variable. In the absence of evidence to the contrary, the skilled artisan would have a reasonable expectation of success in obtaining a DNA sequence utilizing capillaries of 0.5 or 0.2 mm. Thus, the instantly claimed system is prima facie obvious.

Conclusion

12. Claims 1-18, 20-21, and 24-26 are pending. Claims 1-2, 11-14, and 24-26 are drawn to a nonelected invention. Claims 3-10, 15-18, and 20-21 are rejected. No claims are allowed.

Contacts

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick T. Lewis whose telephone number is 703-305-4043. The examiner can normally be reached on M-F 8:00 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 703-308-4624. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Patrick T. Lewis, PhD
Examiner
Art Unit 1623

James O. Wilson
Supervisory Patent Examiner
Technology Center 1600

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June 15, 2003